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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,500	04/07/1999	JOHN C. LEE	STK-1-DIV-3	6377

7590 07/12/2004

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/287,500	LEE ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-73,102,106,108-110 and 112-122* is/are pending in the application.

4a) Of the above claim(s) *70,72,73 and 118-122* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69,71,102,106,108-110 and 112-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *69-73,102,106,108-110 and 112-122* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 04/19/2004 has been entered. Claims 69-73, 102, 106, 108-110, 112-122 are pending. Applicant's election with traverse of group I, claims 69-73 and 102 to the extent that they are drawn to a method of inducing local tissue formation comprising implanting a morphogenic protein and IGF-I, in Paper No. 21 is acknowledged. Claims 118-122 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 21. Applicant's election of the species bone defect locus, the species fracture, and the species BMP-7 in Paper No. 21 is acknowledged. Claims 70, 72, 73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 69, 71, 102, 106, 108-110, 112-117 are being examined to the extent that they read upon a method of inducing local tissue formation comprising implanting a morphogenic protein and IGF-I, and the species bone defect locus, the species fracture, and the species BMP-7.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 102

Claims 69, 71, 106, 108-110, 112, 114, 115 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (B, Paper No. 7). Applicants argue that the amended claims do not recite BMP-2. Applicant's arguments have been fully considered but they are not persuasive. Wang intends the designation "BMP-2" to encompass both BMP-2A and BMP-2B (paragraph bridging columns 3-4). Wang teaches that BMP-2s, such as

BMP-2A and BMP-2B, may be combined with IGF-I. BMP-2B is an alternate designation for BMP-4, as evidenced by Wang (column 2, lines 17-20; column 3, lines 47-50). The amended claims recite BMP-4.

Claim Rejections - 35 USC § 103

Claims 69, 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (B, Paper No. 7) in view of Kuberasampath (N, Paper No. 11).

Applicants argue that Kuberasampath does not disclose a heparin carrier as indicated by the examiner, because the heparin is crosslinked to the collagen. Applicant's arguments have been fully considered but they are not persuasive. The only disclosure of a heparin carrier in the present application is in the context of WO91/18558 (see page 48, line 13, through page 50, line 11, of the present specification), which is the Kuberasampath reference that is cited in the present rejection. Further, the present specification at page 48, line 13, through page 50, line 11, discloses that the heparin can be crosslinked to the collagen. The examiner therefore concludes that the heparin carrier in the claimed method and the heparin carrier disclosed by Kuberasampath are the same. Furthermore, Wang intends the designation "BMP-2" to encompass both BMP-2A and BMP-2B (paragraph bridging columns 3-4). Wang teaches that BMP-2s, such as BMP-2A and BMP-2B, may be combined with IGF-I. BMP-2B is an alternate designation for BMP-4, as evidenced by Wang (column 2, lines 17-20; column 3, lines 47-50). The amended claims recite BMP-4.

Claims 69, 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (b7).

Applicants argue that Wang does not teach or suggest that IGF-I, hydrocortisone, insulin, or PTH synergizes with "BMP-4, ... and COP-7." Applicant's arguments have been fully considered but they are not persuasive. Wang intends the designation "BMP-2" to encompass both BMP-2A and BMP-2B (paragraph bridging columns 3-4). Wang teaches that BMP-2s, such as BMP-2A and BMP-2B, may be combined with IGF-I. BMP-2B is an alternate designation for BMP-4, as evidenced by Wang (column 2, lines 17-20; column 3, lines 47-50). The amended claims recite BMP-4.

Claims 69, 113, 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (B, Paper No. 7), as applied to claim 69 above, and further in view of Kuberasampath (E, Paper No. 7) and Reddi (V, Paper No. 24).

Applicants argue that Wang does not teach or suggest that the activity of any BMP other than BMP-2 may be synergized by IGF-I, that nothing in the cited references would provide the skilled artisan with a reasonable expectation of success, that Applicants have demonstrated that some of the growth factors disclosed in Kuberasampath and Reddi do not act synergistically with a morphogenetic protein. Applicant's arguments have been fully considered but they are not persuasive.

Wang intends the designation "BMP-2" to encompass both BMP-2A and BMP-2B (paragraph bridging columns 3-4). Wang teaches that BMP-2s, such as BMP-2A and BMP-2B, may be combined with IGF-I. BMP-2B is an alternate designation for BMP-4, as evidenced by Wang (column 2, lines 17-20; column 3, lines 47-50).

The fact that BMP-2 may act in concert with or perhaps synergistically with a growth factor such as IGF-I, the fact that the initiation of bone formation by BMPs is promoted by IGF-1, that fact that OP-1 is a useful morphogen, and the fact that OP-1 may be administered together with other "co-factors," such as IGF-I, known to have a beneficial effect on bone remodeling, creates a reasonable expectation that the combination of OP-1 and IGF-I is synergistic.

The examiner does not agree with Applicants' characterization of what the present application demonstrates. The present specification only shows the induction of AP activity. AP is not the sole determinate of bone induction in vivo. This is also obvious from the specification's disclosure (page 39, full paragraph 2) wherein the data summarized in FIG. 12 indicate that TGF-β is not a MPSF in combination with OP-1 in the AP activity assay in FRC cells in vitro. TGF-β alone did not stimulate AP activity. TGF-β (0.05-3.0 ng/ml) did not exhibit any synergistic effect with OP-1 on AP activity. However, TGF-β and BMP synergize in promoting formation of endochondral bone in vivo. See Ogawa (u11), page 14233, paragraph bridging columns 1-2. Although all combinations of BMPs and growth factors may not synergistically enhance AP activity, the claims are not limited to the synergistic enhancement of AP activity

Claim Rejections - 35 USC § 112

Claims 69, 71, 102, 106, 108-110, 112-117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the specification provides various examples describing animal models for testing tissue formation, that these models are predictive of tissue formation in the human patient, that the alkaline phosphatase activity is predictive of bone formation, that the Lee declaration demonstrates that the combination of OP-1 and IGF-I synergistically induces alkaline phosphatase activity in BAC cells. Applicant's arguments have been fully considered but they are not persuasive.

Although the results with various animal models of bone induction may be reasonably predictive of bone induction in vivo, the present specification only demonstrates an enhancement of AP activity in vitro. However, the use of in vitro assay systems has proven not to be predictive of bone formation in vivo. See Wozney (U), paragraph bridging pages 726-727. This is also obvious from the specification's disclosure (page 39, full paragraph 2) wherein the data summarized in FIG. 12 indicate that TGF-β is not a MPSF in combination with OP-1 in the AP activity assay in FRC cells in vitro. TGF-β alone did not stimulate AP activity. TGF-β (0.05-3.0 ng/ml) did not exhibit any synergistic effect with OP-1 on AP activity. However, TGF-β and BMP synergize in promoting formation of endochondral bone in vivo. See Ogawa (U, Paper No.), page 14233, paragraph bridging columns 1-2. Thus, the in vitro assay of AP activity is not predictive of synergistic enhancement of bone formation in vivo.

The declaration under 37 CFR 1.132 filed 04/19/2004 is insufficient to overcome the rejection of claims 69, 71, 102, 106, 108-110, 112-117 based upon a lack of

enablement under 35 U.S.C. § 112, first paragraph, as set forth in the last Office action because: the declaration provides additional evidence that OP-1 and IGF-I enhance AP activity in a BAC cell assay. The declaration does not provide any evidence that AP activity in vitro is predictive of synergistic enhancement of bone, cartilage, tendon/ligament, and neural tissue in vivo. The examiner has already noted that the use of in vitro assay systems has proven not to be predictive of bone formation in vivo. See Wozney (U), paragraph bridging pages 726-727. Furthermore, the present specification demonstrates that TGF-β (0.05-3.0 ng/ml) did not exhibit any synergistic effect with OP-1 on AP activity. However, TGF-β and BMP synergize in promoting formation of endochondral bone in vivo. See Ogawa (U, Paper No.), page 14233, paragraph bridging columns 1-2. Thus, the in vitro assay of AP activity is not predictive of in vivo tissue formation. Although Dr. Lee expresses the opinion that the in vitro assay of AP activity is predictive of in vivo tissue formation, this is merely a conclusory statement and is not found to be of substantial evidentiary value. Conclusory statements without any articulated rationale or evidentiary support, do not constitute sufficient factual findings.

Double Patenting

Claims 69, 71, 102, 106, 108-110, 112-117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,048,964. It is acknowledged that Applicants are ready to submit a terminal disclaimer when the present claims are found allowable.

Claims 69, 71, 102, 106, 108-110, 112-117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 5948428. It is acknowledged that Applicants are ready to submit a terminal disclaimer when the present claims are found allowable.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571)272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

5

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JULY 11, 2004